



PATENT

THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

JAMES J. BENEDICT ET AL.

Serial No.: 09/748,038

Filed: December 22, 2000

For: METHOD OF PROMOTING NATURAL
BYPASS

Group Art Unit: 1654

Examiner: Jeffrey E. Russel

Attorney Docket: 2103.013900/RFE
(SBI-042-CIP)

CUSTOMER NO. 45488

**DECLARATION OF JAMES J. BENEDICT, JOHN P. RANIERI, MARSHA ROLLE,
AND RAMA AKELLA UNDER 37 C.F.R. 1.131**

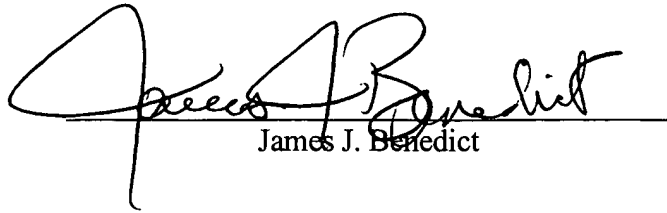
We, James J. Benedict, John P. Ranieri, Marsha Rolle (née Whitney), and Rama Akella,
state as follows:

1. We are the inventors of the above-identified patent application.
2. We may herein refer to Exhibits 1-3 which were previously filed in this application with the declaration of Rama Akella dated June 13, 2005.
3. Exhibit 4 (attached hereto) is a copy of a letter sent from Wilfried Roethy and Daniel Burkhoff of Columbia University to one of us (John P. Ranieri) at a date prior to March 31, 2000.
4. We were employees of Sulzer Innotec, Ltd., or its corporate successors as of the date of the letter presented in Exhibit 4.

5. The letter presented in Exhibit 4 enclosed copies of photographs of histologic slides taken from dogs used in the research project established between Sulzer Innotec and Columbia University as shown in Exhibit 1 and continued as shown in Exhibit 2.
6. The histologic slide photograph at p. 4, upper right, of Exhibit 4 was reused as Figure 2D of the article by Roethy et al. previously presented as Exhibit 3. The histologic slide photographs of p. 5, right hand column, of Exhibit 4 were reused (from top to bottom) as Figures 2A-C of Exhibit 3.
7. The successful induction of angiogenesis prior to March 31, 2000, as shown by Exhibit 4, is indicated by Exhibit 3, p. 496, left col., Pilot Study: "In GF_m (1.0 mg/ml)-treated animals allowed to survive for 2 weeks, large, BrdU-positive, conduit-sized vessels with diameters up to 300 μ m could be detected in areas surrounding the injection sites, both in ischemic and nonischemic areas of the heart (Fig. 2, A-D)."
8. As demonstrated by the results shown in Exhibit 4, in light of previously presented Exhibits 1-3, we conceived of, tested, and showed success for methods of promoting natural bypass, promoting vessel growth, or treating ischemic tissue damage in a mammal (in this example, dog) comprising administering to the mammal a mixture of proteins derived from ground bone (in this example, GF_m) prior to March 31, 2000.
9. Our work was performed in the United States of America.
10. We declare that all statements made of our own knowledge are true and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of title 18 of

the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 11/18/2005


James J. Benedict

Date: _____

John P. Ranieri

Date: _____

Marsha Rolle

Date: _____

Rama Akella



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

JAMES J. BENEDICT ET AL.

Serial No.: 09/748,038

Filed: December 22, 2000

For: METHOD OF PROMOTING NATURAL
BYPASS

Group Art Unit: 1654

Examiner: Jeffrey E. Russel

Attorney Docket: 2103.013900/RFE
(SBI-042-CIP)

CUSTOMER NO. 45488

**DECLARATION OF JAMES J. BENEDICT, JOHN P. RANIERI, MARSHA ROLLE,
AND RAMA AKELLA UNDER 37 C.F.R. 1.131**

We, James J. Benedict, John P. Ranieri, Marsha Rolle (née Whitney), and Rama Akella,
state as follows:

1. We are the inventors of the above-identified patent application.
2. We may herein refer to Exhibits 1-3 which were previously filed in this application with the declaration of Rama Akella dated June 13, 2005.
3. Exhibit 4 (attached hereto) is a copy of a letter sent from Wilfried Roethy and Daniel Burkhoff of Columbia University to one of us (John P. Ranieri) at a date prior to March 31, 2000.
4. We were employees of Sulzer Innotec, Ltd., or its corporate successors as of the date of the letter presented in Exhibit 4.

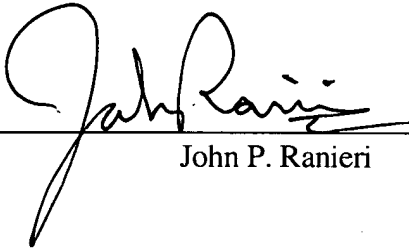
5. The letter presented in Exhibit 4 enclosed copies of photographs of histologic slides taken from dogs used in the research project established between Sulzer Innotec and Columbia University as shown in Exhibit 1 and continued as shown in Exhibit 2.
6. The histologic slide photograph at p. 4, upper right, of Exhibit 4 was reused as Figure 2D of the article by Roethy et al. previously presented as Exhibit 3. The histologic slide photographs of p. 5, right hand column, of Exhibit 4 were reused (from top to bottom) as Figures 2A-C of Exhibit 3.
7. The successful induction of angiogenesis prior to March 31, 2000, as shown by Exhibit 4, is indicated by Exhibit 3, p. 496, left col., Pilot Study: "In GF_m (1.0 mg/ml)-treated animals allowed to survive for 2 weeks, large, BrdU-positive, conduit-sized vessels with diameters up to 300 μ m could be detected in areas surrounding the injection sites, both in ischemic and nonischemic areas of the heart (Fig. 2, A-D)."
8. As demonstrated by the results shown in Exhibit 4, in light of previously presented Exhibits 1-3, we conceived of, tested, and showed success for methods of promoting natural bypass, promoting vessel growth, or treating ischemic tissue damage in a mammal (in this example, dog) comprising administering to the mammal a mixture of proteins derived from ground bone (in this example, GF_m) prior to March 31, 2000.
9. Our work was performed in the United States of America.
10. We declare that all statements made of our own knowledge are true and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of title 18 of

the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: _____

James J. Benedict

Date: 12/19/05



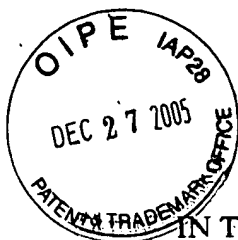
John P. Ranieri

Date: _____

Marsha Rolle

Date: _____

Rama Akella

**PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

JAMES J. BENEDICT ET AL.

Serial No.: 09/748,038

Filed: December 22, 2000

For: METHOD OF PROMOTING NATURAL
BYPASS

Group Art Unit: 1654

Examiner: Jeffrey E. Russel

Attorney Docket: 2103.013900/RFE
(SBI-042-CIP)**CUSTOMER NO. 45488****DECLARATION OF JAMES J. BENEDICT, JOHN P. RANIERI, MARSHA ROLLE,
AND RAMA AKELLA UNDER 37 C.F.R. 1.131**

We, James J. Benedict, John P. Ranieri, Marsha Rolle (née Whitney), and Rama Akella,
state as follows:

1. We are the inventors of the above-identified patent application.
2. We may herein refer to Exhibits 1-3 which were previously filed in this application with the declaration of Rama Akella dated June 13, 2005.
3. Exhibit 4 (attached hereto) is a copy of a letter sent from Wilfried Roethy and Daniel Burkhoff of Columbia University to one of us (John P. Ranieri) at a date prior to March 31, 2000.
4. We were employees of Sulzer Innotec, Ltd., or its corporate successors as of the date of the letter presented in Exhibit 4.

5. The letter presented in Exhibit 4 enclosed copies of photographs of histologic slides taken from dogs used in the research project established between Sulzer Innotec and Columbia University as shown in Exhibit 1 and continued as shown in Exhibit 2.
6. The histologic slide photograph at p. 4, upper right, of Exhibit 4 was reused as Figure 2D of the article by Roethy et al. previously presented as Exhibit 3. The histologic slide photographs of p. 5, right hand column, of Exhibit 4 were reused (from top to bottom) as Figures 2A-C of Exhibit 3.
7. The successful induction of angiogenesis prior to March 31, 2000, as shown by Exhibit 4, is indicated by Exhibit 3, p. 496, left col., Pilot Study: "In GF_m (1.0 mg/ml)-treated animals allowed to survive for 2 weeks, large, BrdU-positive, conduit-sized vessels with diameters up to 300 μ m could be detected in areas surrounding the injection sites, both in ischemic and nonischemic areas of the heart (Fig. 2, A-D)."
8. As demonstrated by the results shown in Exhibit 4, in light of previously presented Exhibits 1-3, we conceived of, tested, and showed success for methods of promoting natural bypass, promoting vessel growth, or treating ischemic tissue damage in a mammal (in this example, dog) comprising administering to the mammal a mixture of proteins derived from ground bone (in this example, GF_m) prior to March 31, 2000.
9. Our work was performed in the United States of America.
10. We declare that all statements made of our own knowledge are true and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of title 18 of

the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: _____

James J. Benedict

Date: _____

John P. Ranieri

Date: 12/20/05



Marsha Rolle

Date: _____

Rama Akella



PATENT

THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

JAMES J. BENEDICT ET AL.

Serial No.: 09/748,038

Filed: December 22, 2000

For: METHOD OF PROMOTING NATURAL
BYPASS

Group Art Unit: 1654

Examiner: Jeffrey E. Russel

Attorney Docket: 2103.013900/RFE
(SBI-042-CIP)

CUSTOMER NO. 45488

**DECLARATION OF JAMES J. BENEDICT, JOHN P. RANIERI, MARSHA ROLLE,
AND RAMA AKELLA UNDER 37 C.F.R. 1.131**

We, James J. Benedict, John P. Ranieri, Marsha Rolle (née Whitney), and Rama Akella,
state as follows:

1. We are the inventors of the above-identified patent application.
2. We may herein refer to Exhibits 1-3 which were previously filed in this application with the declaration of Rama Akella dated June 13, 2005.
3. Exhibit 4 (attached hereto) is a copy of a letter sent from Wilfried Roethy and Daniel Burkhoff of Columbia University to one of us (John P. Ranieri) at a date prior to March 31, 2000.
4. We were employees of Sulzer Innotec, Ltd., or its corporate successors as of the date of the letter presented in Exhibit 4.

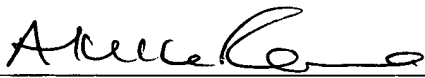
5. The letter presented in Exhibit 4 enclosed copies of photographs of histologic slides taken from dogs used in the research project established between Sulzer Innotec and Columbia University as shown in Exhibit 1 and continued as shown in Exhibit 2.
6. The histologic slide photograph at p. 4, upper right, of Exhibit 4 was reused as Figure 2D of the article by Roethy et al. previously presented as Exhibit 3. The histologic slide photographs of p. 5, right hand column, of Exhibit 4 were reused (from top to bottom) as Figures 2A-C of Exhibit 3.
7. The successful induction of angiogenesis prior to March 31, 2000, as shown by Exhibit 4, is indicated by Exhibit 3, p. 496, left col., Pilot Study: "In GF_m (1.0 mg/ml)-treated animals allowed to survive for 2 weeks, large, BrdU-positive, conduit-sized vessels with diameters up to 300 µm could be detected in areas surrounding the injection sites, both in ischemic and nonischemic areas of the heart (Fig. 2, A-D)."
8. As demonstrated by the results shown in Exhibit 4, in light of previously presented Exhibits 1-3, we conceived of, tested, and showed success for methods of promoting natural bypass, promoting vessel growth, or treating ischemic tissue damage in a mammal (in this example, dog) comprising administering to the mammal a mixture of proteins derived from ground bone (in this example, GF_m) prior to March 31, 2000.
9. Our work was performed in the United States of America.
10. We declare that all statements made of our own knowledge are true and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of title 18 of

the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: _____
James J. Benedict

Date: _____
John P. Ranieri

Date: _____
Marsha Rolle

Date: December 19, 2005

Rama Akella

To
Sulzer Innotec
c/o John P. Ranieri, Ph.D.
Director
CarboMedics
1300-B East Anderson Lane
Austin, Texas 78752

RECEIVED

WILLIAMS, MORGAN & AMERSON

Dear Dr. Ranieri,

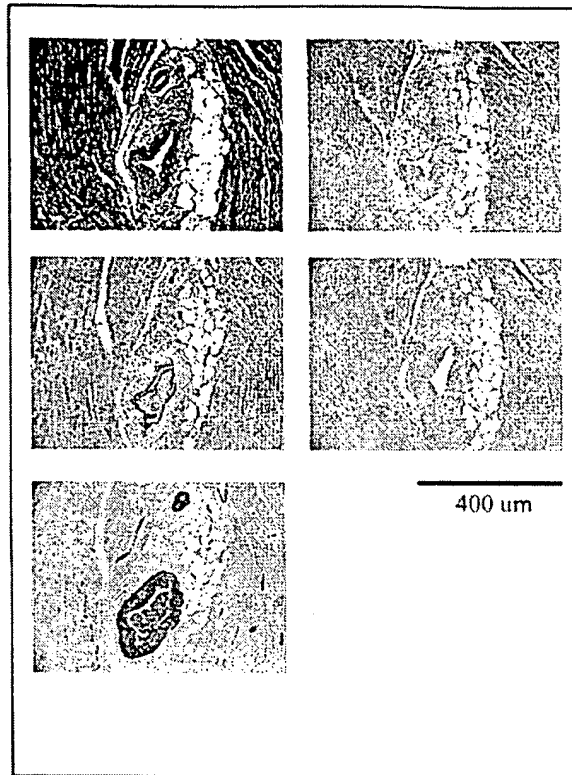
Please find enclosed the first series of the histologic slides, we were talking about this morning. We grouped together pictures of the same vessels with different staining. In addition to the color prints, there is a separate page from the laser printer with the corresponding legends.
We hope, that these pictures will be useful for your meeting.

Wishing you happy holidays,

Sincerely yours,


Wilfred Roethy, M.D.

Daniel Burkhoff, M.D., Ph.D.



Overview:

Dog # 2, 2 weeks survivor

GF: none, Povidone carrier, ischemic area

Staining:

(left side, from top to bottom):

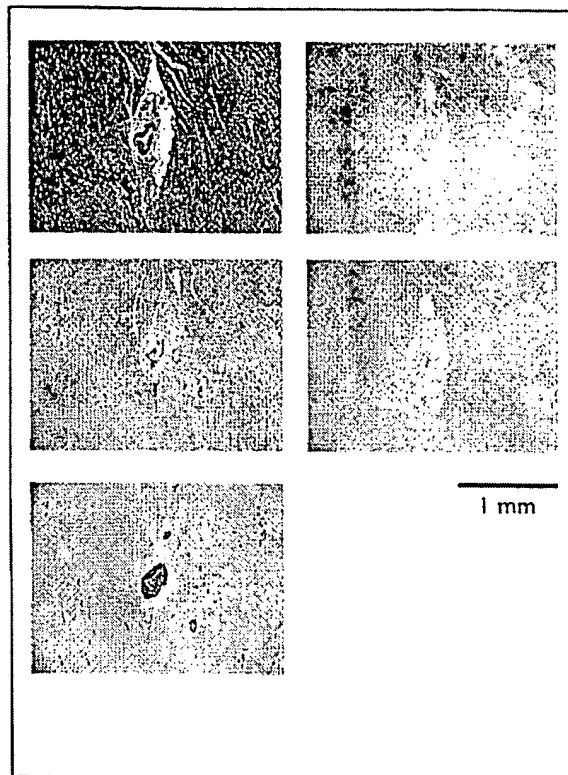
Trichrome, Factor VIII, SMA

(right side, from top to bottom):

PCNA, BrdU

original magnification 100x

BEST AVAILABLE COPY



Overview:

Dog # 2, 2 weeks survivor

GF: none, Povidone carrier, ischemic area

Staining:

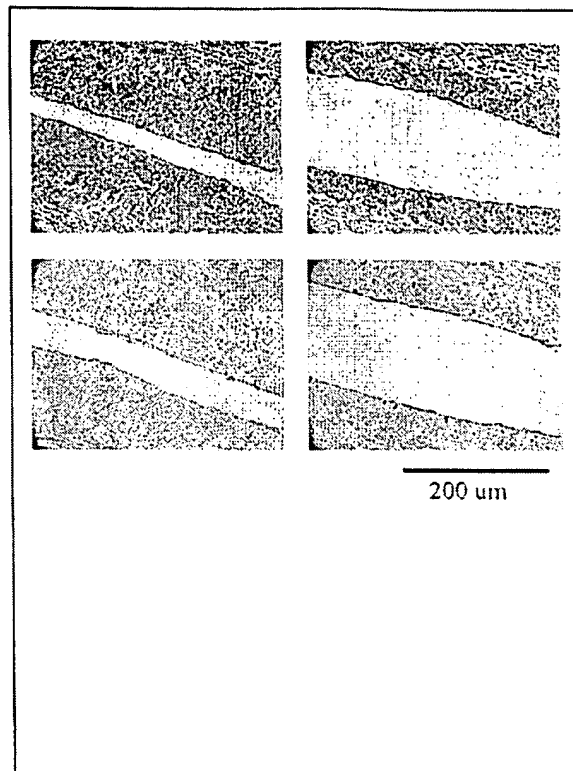
(left side, from top to bottom):

Trichrome, Factor VIII, SMA

(right side, from top to bottom):

PCNA, BrdU

original magnification 40x



Overview:

Dog # 2, 2 weeks survivor

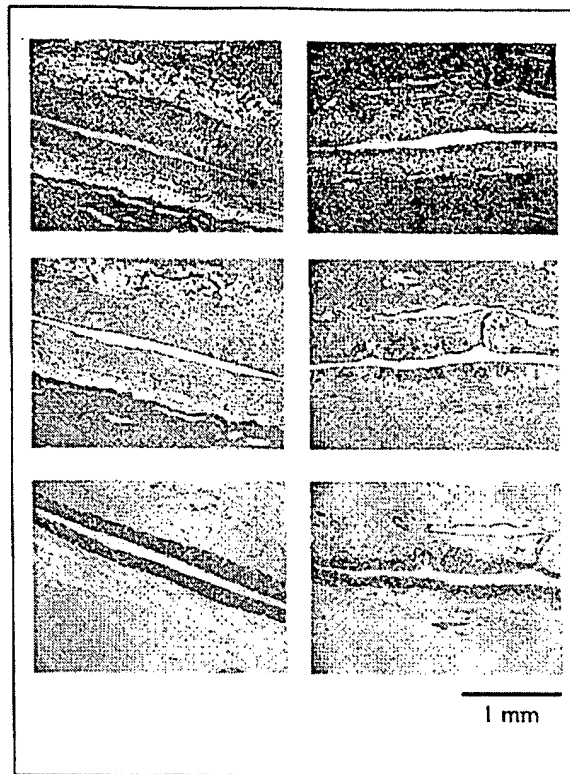
GF: high concentration, Povidone carrier, non ischemic area

left side: vessel A, right side: vessel B

Staining (from top to bottom):

PCNA, BrdU

original magnification 200x



Overview:

Dog # 2, 2 weeks survivor,

GF: high concentration, Povidone carrier, non ischemic area

left side: vessel A, right side: vessel B

Staining (from top to bottom):

Trichrome, Factor VIII, SMA

original magnification 40x

BEST AVAILABLE COPY